Hyperglycaemia due to Insulin Resistance Caused by Interferon-γ

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Marked hyperglycaemia (30.9 mmol l^{-1}) during interferon-γ (IFN-γ) therapy for asymptomatic recurrent renal cancer as multiple lung metastases in a 52-year-old man is described. Although the involvement of IFN-γ has been reported in the development of autoimmune diabetes, in this case, antibodies against pancreatic β-cells including anti-islet cell antibody (ICA) and anti-glutamic acid decarboxylase (GAD) antibody were negative. Moreover, serum level of immunoreactive insulin (IRI) (11 μU ml^{-1} at fasting) and urinary excretion of C-peptide (108 μ g day^{-1}, reference range: 20–130) suggested insulin resistance, supported by results of insulin tolerance tests. With insulin therapy and cessation of IFN-γ, fasting blood glucose concentration returned to 6.2 mmol l^{-1}, and insulin therapy was discontinued. The injection of IFN-γ may cause hyperglycaemia because of insulin resistance, rather than β-cell injury. © **1998 John Wiley & Sons, Ltd.**

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Introduction

Interferon-γ (IFN-γ) is involved in many immune and inflammatory processes, and may play a role in the pathogenesis of autoimmune diabetes mellitus by activating the cytotoxic T-cells which destroy pancreatic β-cells.[1] Insulin resistance as well as impaired insulin secretion contribute to hyperglycaemia in Type 2 (non-insulin-dependent) diabetes mellitus.[2] Interferons have been reported to induce insulin resistance during viral infections.[3,4] As interferons are increasingly used for a variety of diseases, a growing number of reports on their adverse effects, including onset of diabetes,[5,6] is being published. We report a case of hyperglycaemia during IFN-γ therapy, which appeared to be related to insulin resistance.

Case Report

A 52-year-old man was admitted to our hospital because of metastatic lung disease. Biopsy showed a clear cell carcinoma, identical to a renal cancer which had been resected 12 years earlier. Interferon-γ (recombinant, Shionogi, Japan) was injected (300 million IU day^{-1} for 5 days, followed by 600 million IU day^{-1} for 4 days). The patient, who was not obese (BMI 23), had been known to have impaired glucose tolerance for 4 years. His only medication was captopril, diltiazem and bezafibrate, all of which were continued throughout his admission. On admission, he had no symptoms either related to his tumour or to suggest diabetes. His postprandial blood glucose value was 9.6 mmol l^{-1} on admission. Hyperglycaemia was found (maximum: 30.9 mmol 1^{-1} before dinner) on day 7 of the IFN-γ therapy. At this time, the amount of urine C-peptide was 108 μg day^{-1} (average of 3 days) and fasting serum IRI was 11 μU ml^{-1}. The normal ranges for urinary C-peptide 20–130 μg day^{-1} and serum creatinine was 106 μmol l^{-1} (reference range 62–97). Free-triiodothyronine was 3.3 ng l^{-1} (2.0–6.0), thyroxine 68 μg l^{-1} (40–120), growth hormone 0.25 μg l^{-1} (0–5), adrenaline <7 ng l^{-1} (0–80), noradrenaline 291 ng l^{-1} (90–420), cortisol 169 μg l^{-1} (50–150), and pancreatic glucagon 191 ng l^{-1} (70–160). ICA and anti-GAD antibody were negative. His HLA-type was DRW15, DR9, DRW53, DQW6, DQW9.

Subcutaneous insulin injection was started on day 7 and IFN-γ therapy stopped on day 9. The dose of insulin was increased gradually to 50 U day^{-1} (0.77 U kg^{-1}), and his fasting blood glucose value was 7.4 mmol l^{-1} on day 18. The insulin tolerance tests were performed on day 14 and on day 26 (Table 1), suggesting the presence of insulin resistance on day 14 and its improvement on day 26. Finally, the amount of urine C-peptide significantly decreased to 65 μg day^{-1} (average of 3 days) and there was no longer any need for insulin injections after day 31. Captopril was also stopped at this time, because of normotension. Serum concentrations of TNF-α were examined retrospectively from stored frozen samples. They had been collected before the treatment of IFN-γ, at the finding of hyperglycaemia, and after the cessation

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Table 1. Results of insulin tolerance test; 0.1 U kg^{-1} of insulin was injected intravenously and blood glucose value (mmol l^{-1}) was examined.

	Fasting	15 min	30 min	60 min
Day 14	13.3	11.9	10.3	9.5[a]
Day 26	5.4	4.3	3.1[b]	3.6

[a]71 % of the fasting, [b]57 % of the fasting.

of insulin therapy. All the values were below the detectable range in the serum (<5 ng l^{-1}).

Discussion

One of the characteristics of autoimmune destructive insulitis is a high production of IFN-γ by infiltrating T-cells.[1] The expression of IFN-γ in the pancreatic β-cells has also been reported to induce diabetes by β-cell destruction in transgenic mice.[7] In one study in man, increased serum IFN-γ was seen more frequently in patients with autoimmune diabetes than in non-diabetic controls.[8] IFN-α has been associated with induction of diabetes with occurrence of autoantibodies against β-cells.[5,6] In contrast, in the present case, IFN-γ appeared to aggravate insulin resistance and cause hyperglycaemia with insulin resistance rather than by β-cell injury. The autoantibodies characteristic of autoimmune diabetes were not detectable; there was a poor response to an insulin tolerance test; urine C-peptide excretion suggested that IFN-γ did not induce impaired secretion of insulin. Our patient had only one kidney and a marginally elevated creatinine suggestive of a low glomerular filtration rate, so the amount of insulin secretion may even have been underestimated.

We suggest that injection of IFN-γ produced an inflammatory reaction and insulin resistance either directly or indirectly through stimulated cytokines. TNF-α is a cytokine which has been associated with insulin resistance[9] and its secretion is believed to be stimulated by the injection of IFN-γ. Although the serum levels of TNF-α were not detectable in our patient, the possibility that IFN-γ affected local TNF-α concentration around the adipose tissue and caused insulin resistance cannot be excluded. To our knowledge, this is the first report describing the induction of hyperglycaemia associated with the injection of IFN-γ. The mechanism of IFN-γ's variant effects on glucose metabolism needs to be elucidated.

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